REMARKS

Applicants respectfully request consideration of the foregoing amendments and the following commentary upon reexamination of the present application on the merits.

I. Status of the Claims

Claims 1-15, 17 and 21-27 were cancelled previously. Claim 16 has been amended for greater clarity, in conformance with the Examiner's suggestions. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 16, 18-20, and 28-32 will be pending.

II. Rejection of Claims under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 16, 18-20 and 28-32 for alleged indefiniteness. More specifically, the Examiner alleges that recitation of "mutations" in claim 16 lacks any antecedent basis. The term "mutations" has been deleted. Accordingly, reconsideration and withdrawal of the rejection are requested.

III. Rejection of Claims under 35 U.S.C. §112, first paragraph

The Examiner maintained the rejection of claims 16, 18-20 and 28-32 for alleged lack of enablement. Applicants respectfully traverse the rejection.

Without acquiescing to the stated rationale of rejection, claims 16 and 19 have been amended to track the language that the Examiner recommended in the paragraph at page 4 of the final Office Action. Since the Examiner has acknowledged that the specification is enabling for the herpes simplex virus as presently claimed, Applicants respectfully request withdrawal of the rejection.

IV. Rejection of Claims under 35 U.S.C. §103(a)

A. Roizman and Vile

Claims 16, 28 and 29 remain rejected over U.S. Patent No. 6,172,047 to Roizman et al. ("Roizman") in view of Vile et al., *Ann. Oncol.* 5 Suppl. 4: 59-65, 1994 ("Vile"). Applicants respectfully traverse the rejection of the remaining claims.

In advancing the rejection, the Examiner relies on the primary reference, Roizman, for the alleged teaching of using γ-34.5 minus HSV-1 as a therapeutic agent for tumororgenic diseases. The secondary reference, Vile, is cited for the alleged teaching of exogenous expression of a cytokine gene.

Roizman actually would have informed the skilled artisan only that an HSV mutant may be used in oncolytic therapy, since the mutant HSV is able to infect dividing cells, such as cancer cells, while leaving the normal, undividing cells unharmed. On the other hand, Vile taught *in situ* gene therapy using cytokines, but the reference would not have suggested expression of a cytokine in the context of an oncolytic virus such as HSV. That is, Vile discloses direct injection of cytokine-encoding DNA, under the control of a tumor-specific promoter, into established tumors of mice, resulting in cytokine expression (see "Summary" and Figures 4b and 4c). Vile concludes that "[n]o statistically significant reduction in tumor growth was seen following injection of any of these cytokine expression plasmids..." (page S62, right column, lines 9-12 and figure 4a).

Vile was published in 1994; hence, it evidences the state of the art at the priority date of the present application. At the time of publication, according to Vile, "such in situ gene therapy [as described above] would require a specificity of gene delivery that is ***impossible using currently available viral vectors*** or physical transfer techniques" ("Introduction" at page S59, left column in lines 12-15; emphasis added). Vile attempted to address this contemporaneous "impossibility" by using a tumor-specific promoter to direct expression of cytokine genes, but be failed to achieve any therapeutic effects, as noted above. Thus, Vile admitted that, "[t]o date, a significant anti-tumor

effect on the growth of the injected tumors using cytokine cDNAs has not been observed," and that "[t]his is not wholly unexpected" (page S64, left column, lines 14-16).

At the time of filing, therefore, the prior art made no suggestion of expressing a cytokine with an oncolytic virus. Indeed, such a combination would have contravened the conventional wisdom of the day and, hence, was anything but obvious.

(1) PTO's combining of cited references is informed by hindsight, not by suggestion in the prior art

As Vile illustrates, classic gene therapy entailed transduction and expression of a foreign gene that has therapeutic effects. The goal of the classical approach was to realize a therapeutic impact by transgenic expression, *per se,* in relation to which neither the generating of viral progeny (replication competence) nor the inducing of apoptosis (oncolysis) had an art-recognized role.

It is apparent, therefore, that the gene-therapy paradigm of the prior art contrasts sharply with the approach of the present invention. The latter employs an oncolytic viral (HSV) vector that is replication-competent; hence, the vector is not a mere delivery vehicle but rather is a *de facto* active agent, killing host cells.

The Examiner can combine the cited references only with the aid of hindsight, therefore. In fact, the principles of (a) long-lasting expression of a transgene, for gene-therapy purposes, and (b) killing host cells by means of a replicating virus not only are drawn from different, essentially unrelated fields of technology but also embody conflicting objectives. That is, long-lasting transgene expression requires an intact target cell, whereas oncolytic therapy aims at the effective destruction of the target cell.

(2) Evidence of record that the purported combination would have contravened conventional wisdom

The foregoing deficiencies are sufficient grounds for withdrawal of this rejection. Still, Applicants also have made of record a Rule 132 declaration by inventor Rabkin, attesting that those in the field would not have considered it obvious to express cytokines in the HSV, given the known protective effects of cytokines for HSV. Rather than contesting the declaration evidence directly, however, the Examiner is heard to contend that the evidence is not probative of patentability because, pursuant to the claimed invention, a cytokine gene would not be expressed until after the HSV vector infected targeted cells.

Again, the Examiner's discounting of the declaration evidence is based on 20/20 hindsight. As explained above, the skilled person would have understood that expression of cytokine and the resultant elicitation of an immune response require the existence of an intact, functioning target cell. On the other hand, infection with an oncolytic HSV of the claimed invention kills the target cell. Thus, the contemporaneous teachings of the cited art (as opposed to the present teachings of Applicants' specification) would have prompted the skilled artisan *not* to consider an "expressible," cytokine-encoding "nucleotide sequence," as presently recited, as a feasible component for a herpes simplex virus vector.

Indeed, the prospect of combining the prior-art teachings invoked by the Examiner would have presented the skilled artisan with several scenarios, each fraught with *a priori* uncertainty:

(A) The expression or secretion of the cytokine could induce an anti-HSV immune response, which threatens the elimination of HSV-infected tumor cells before the HSV replicates and spreads. The oncolytic effect of HSV would be lost as a consequence, and the immune effect would be equivalent to that of a cytokine gene therapy approach where immunization against tumor antigens is intended.

(B) The replication of HSV, leading to apoptosis and/or cell lysis, is rapid enough to parallel an anti-HSV response that the cytokine induces. Accordingly, the virus still is able to spread and, while it alerts the immune system to viral antigens, it also induces an anti-tumor immune response.

(C) The replication of HSV leads to apoptosis or cell lysis before the release of a sufficient amount of expressed cytokine, thereby realizing benefit from oncolytic therapy only.

Which of these scenarios might prevail was entirely unpredictable, in view of contemporaneous state of the art. This lack of predictability also is sufficient unto itself to defeat the notion that the claimed HSV is obvious within the meaning of Section 103.

In view of the foregoing, it is apparent that Applicants' declaration evidence stands effectively unrebutted on the record. For this reason, too, withdrawal of the obviousness rejection in question is warranted.

B. Roizman, Vile and Chang

The Examiner maintained the rejection of claims 16 and 18-20 for alleged obviousness over Roizman in view of Vile and further in view of Chang et al., *Virology* 185: 437-440, 1991 ("Chang"). Applicants respectfully traverse the rejection.

The teachings of Roizman and Vile, as well as the patentability of claim 16, are discussed *supra*. Chang is cited for its alleged teaching of a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene but fails to remedy the deficiencies of Roizman and Vile. Therefore, the cited references do not render claim 16 obvious. Claims 18-20 are dependent from a non-obvious base claim 16, and therefore are non-obvious.

C. **Roizman, Vile, McKay and Wright**

The Examiner maintained rejection of claims 30-32 for alleged obviousness over Roizman taken with Chang, and further in view of PCT publication No. WO 92/14821 by McKay *et al.* ("McKay") and U.S. Patent No. 5,639,656 to Wright, Jr. ("Wright"). Applicants respectfully traverse the rejection.

Each of claims 30-32 ultimately depends from claim 16. Since, as discussed above, claim 16 is non-obvious over the cited art, it follows that claims 30-32 likewise are patentable of that art. Applicants respectfully request withdrawal of the rejection, therefore.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they request and early indication to this effect. Examiner Shen is invited to contact the undersigned directly, should he believe that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, Applicants hereby petition for such extension under 37 CFR § 1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

Date 18 December 2008

By _____ YANG TANG
Reg. No. 55,663
for Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399